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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,055	09/24/2004	Hiroaki Sagawa	1422-0644PUS1	9947

2292 7590 09/03/2009

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EXAMINER	
JUEDES, AMY E	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
09/03/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/509,055	SAGAWA ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,12,14-29,31-35 and 37-39* is/are pending in the application.

4a) Of the above claim(s) *8 and 14-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 10, 12, 28-29, 31-35, and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 6/23/09 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/23/09 has been entered.

Claims 1 and 28-29 have been amended.

Claim 30 has been cancelled.

Claims 37-39 have been added.

Claims 1-8, 10, 12, 14-29, 31-35, and 37-39 are pending.

Claims 8 and 14-27 stand withdrawn from further consideration pursuant to 37 CFR 1.14209 as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 1-7, 10, 12, 28-29, 31-35, and 37-39 are under examination.

2. The previous grounds of rejection are withdrawn In view of Applicant's amendment to the claims to recite that the cytotoxic activity is evaluated as the cytotoxic activity against a labeled target cell.

3. The following are new grounds of rejection.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-7, 10, 12, 28-29, 33-35, and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stohl et al., 1990, in view of Cardarelli et al., 1991 (of record), U.S. Patent 5,198,423 (of record), Ybarrondo et al., 1997, and Neri et al., 2001.

Stohl et al. teach a method of differentiating and cytotoxic T lymphocytes (i.e. CD8+ cells) comprising culturing PBMCs with anti-CD3 and IL-2 (see page 3718-3719, in particular). Stohl et al. teach that culturing for 3 days results in the greatest CTL activity (see page 3721 in particular). Stohl et al. teach evaluating cytotoxicity using a radioactively labeled target cell (see page 3719, in particular).

Stohl et al. do not teach incubating the cells with a recombinant fibronectin fragment comprising SEQ ID NO: 12, nor evaluating cytotoxicity using calcein-AM labeled target cells.

Cardarelli et al. teach that the addition of immobilized fibronectin to PBMC cultures stimulated with anti-CD3 and IL-2 enhances expansion and IL-2R expression of T lymphocytes. Cardarelli et al. further teach that the regions of fibronectin responsible for its activity on T cells are the RGD cell binding domain and the EILDV amino acid sequence (see page 115, in particular). Cardarelli et al. also teach that the cells can be cultured at a concentration of 10^5 cells/well of a microtiter plate (i.e. at a concentration between 1 and 5 x 10^5 cells/ml). Ybarrondo et al. teach that immobilized fibronectin provides a costimulatory signal to CTL, that induces an enhanced degranulation response after TCR crosslinking. Ybarrondo et al. teach that degranulation is a mechanism by which CTL lyse target cells.

The '423 patent teaches a biologically active recombinant fibronectin fragment comprising SEQ ID NO: 12 (see columns 3-4 in particular). Said fragment comprises the RGD and EILDV sequences (see columns 3-4 in particular). The '423 patent also teaches that the recombinant fibronectin is advantageous compared to natural fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses (see column 1 in particular).

Neri et al. teach a method of evaluating CTL activity by labeling target cells with calcein-AM, and detecting fluorescence released by lysed target cells (i.e. determining fluorescent intensity ascribed to destroyed target cells, see page 1131, in particular). Neri et al. teach that the method is convenient, rapid, and sensitive, and avoids the problems associated with handling and disposal of radioactive materials (see page 1131, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include immobilized fibronectin, as taught by Cardarelli et al. and Ybarrondo et al., in the method of differentiating CTL taught by Stohl et al. The ordinary artisan would have been motivated to do so, since Cardarelli et al. teach that fibronectin enhances the expansion of T cells cultivated under conditions identical to those of Stohl et al. Furthermore, the ordinary artisan would have been further motivated since Ybarrondo et al. teach that fibronectin acts as a costimulatory molecule for CTL, resulting in an enhanced degranulation response (i.e. enhanced or "longer" cytotoxicity towards a target cells). Furthermore, the ordinary artisan would have been motivated to substitute the recombinant fibronectin fragment taught by the '423 patent, for the purified human fibronectin in the method of Ybarrondo et al. or Cardarelli et al., since the '423 patent teaches that the recombinant fibronectin is advantageous compared to natural fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the recombinant fibronectin fragment, since the '423 patent teaches that the recombinant fibronectin is a biologically active fragment, and it comprises the sequences taught by Cardarelli et al. as being important for T cell simulation.

Furthermore, it would have been obvious to replace the radioactive cytotoxicity assay of Stohl et al., with the calcein-AM cytotoxicity assay taught by Neri et al. The ordinary artisan would have been motivated to do so, since Neri et al. teach that the calcein-AM assay is convenient, rapid, and sensitive, and avoids the problems associated with handling and disposal of radioactive materials. Additionally, it would have been obvious to culture the cells in a petri dish, a flask, or a bag, since these are all well known and routine vessels used for performing tissue culture.

6. Claims 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stohl et al., 1990, Cardarelli et al., 1991, U.S. Patent 5,198,423, Ybarrondo et al., 1997, and Neri et al., 2001, as applied to claims 1-7, 10, 12, 28-29, 33-35, and 37-39 above, and further in view of Chen et al., 1994 (of record).

The combined teachings of Stohl et al., Cardarelli et al., U.S. Patent 5,198,423, Ybarrondo et al., and Neri et al are described above.

They do not teach transducing a foreign gene into the T cells.

Chen et al. teach that retroviral transduction of T cells with PKC allows long term growth of the cells in vitro with maintenance of function and specificity, thus providing a useful approach for more easily procuring large numbers of said cells (see pages 3634-3635, in particular).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to further transduce the cytotoxic T lymphocytes made by the method of Stohl et al., Cardarelli et al., U.S. Patent 5,198,423, Ybarrondo et al., and Neri et al, with a retrovirus encoding PKC, as taught by Chen et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do so, and have a reasonable expectation of success, since Chen et al. teach that retroviral transduction of T cells with PKC allows long term growth of the cells in vitro with maintenance of function and specificity, thus providing a useful approach for more easily procuring large numbers of said cells.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-7, 10, 12, 28-29, 31-35, and 37-39 are provisionally rejected, on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 8, 15-16, 30, 32, 34, and 36-38 of copending Application No. 10/486,512, in view of Mizobata et al., Chen et al., 1994, and Neri et al., 2001.

The '512 application claims a method for inducing cytotoxic T cells, a method for maintaining cytotoxic T cells, and a method for expanding cytotoxic T cells comprising incubating peripheral blood mononuclear cells with fibronectin and anti-CD3. The '512 application further claims that the fibronectin can be SEQ ID NO: 6, which is identical to

SEQ ID NO:12 of the instant application. Additionally, it would have been obvious to further expand the cells with IL-2, since Mizobata et al. teaches that IL-2 induces proliferation of cytotoxic T cells (see Fig. 1 in particular). The '512 application also claims using immobilized fibronectin. Furthermore, the limitations of the instant claims wherein the concentration of cells is between 1 cell/ml to 5 x 10^5 cells per ml, and wherein culturing is performed for 2-15 days represent obvious variations of the method claimed in the '512 application (see for example, Mizobata et al.) and do not render the instant claims patentably distinct. Moreover, it would have been obvious to transduce the cytotoxic T lymphocyte with a foreign gene, since Chen teaches that retroviral transduction with PKC allows long term growth of cytotoxic T cells in vitro. Furthermore, it would have been obvious to evaluate cytolytic activity with a method comprising determining lysis of target cells labeled with calcien-AM as taught by Neri et al.

This is a provisional obviousness-type double patenting rejection.

9. Claims 1-7, 10, 12, 28-29, 31-35, and 37-39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 20-21 of copending Application No. 10/568,745, in view of Mizobata et al. and Neri et al., 2001.

The '745 application claims a method for preparing a cytotoxic lymphocyte comprising the step of carrying out at least one step selected from induction, maintenance, and expansion of a cytotoxic lymphocyte in the presence of fibronectin or a fragment thereof. The '745 application further claims that the fibronectin fragment comprises SEQ ID NO: 13, which is the same as SEQ ID NO: 12 of the instant application. The '745 application also claims that the fibronectin is immobilized on a substrate and that the concentration of cells is between 1 cell/ml to 5 x 10^5 cells per ml. The '745 application also claims that the lymphocytes can be transfected with a foreign gene using a retrovirus, adenonvirus, or simian virus. Additionally, it would be obvious to further expand the cells with IL-2 and anti-CD3, since Mizobata et al. teach that IL-2 and anti-CD3 induce proliferation of cytotoxic lymphocytes (see Fig. 1 in particular). Additionally, it would have been obvious to use PBMC as the source of the cytotoxic

lymphocytes in the method claimed in the '745 application, since Mizobata et al. teach that cytotoxic lymphocytes can be derived from PBMC. Furthermore, it would have been obvious to evaluate cytolytic activity with a method comprising determining lysis of target cells labeled with calcien-AM as taught by Neri et al,

This is a provisional obviousness-type double patenting rejection.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-4471. The examiner can normally be reached on 7am to 3:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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